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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Tianci Luo et al.	Group Art Unit: 1648
Application No. 09/734,836 Confirmation No. 4435	Examiner: Ulrike Winkler
Filed: December 12, 2000	Atty. Docket No. 2503469.991130
For: BOVINE IMMUNODEFICIENCY VIRUS (BIV) BASED VECTORS	Customer No. *35928* 35928 PATENT TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
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Sir:

I, Sheila Connelly, do hereby declare and state:

1. I have a doctoral degree in Molecular Biology and my postdoctoral training was in RNA Processing.

2. For the past 10 years, I have been working on human gene therapy using viral vectors, and more recently, lentiviral vectors, and have expertise in the development and use in animal models of such gene transfer systems.

3. I read the Final Office Action in the above application in which the

Examiner rejected the claims as obvious over the BIV genome patent, the PCT document relating to FIV and the Temin patent teaching BLV. I read those documents.

4. Prior to December 1999, it was known that the lentiviruses each had unique characteristics that distinguish one from the other various lentiviruses.

5. The lentiviruses are essentially specific for the host. Thus, each lentivirus has mechanisms for virus infection (entry into the cytoplasm, transfer into the nucleus, reverse transcription, integration, and gene expression) that are specific to its particular host cells. Moreover, host cell factors are specific for individual lentiviruses. Hence, each lentivirus must have distinct genes to ensure that specificity.

6. In view of that species specificity, each virus must be dealt with individually without consideration of what worked in another lentivirus, particularly with the goal of having a non-human lentivirus infect and express a transgene in a human cell.

7. Thus, each virus is a unique starting material.

8. As maintained by others, I also believe that the more distantly related two species are, the more likely that what works in one species would not work in the other. Conversely, with two more similar species, one might suspect that there's a greater possibility that what works in one species might work in the other.

9. In this regard, CAEV and Visna lentiviruses are more closely related to FIV than is BIV. Yet it has not been possible to generated effective vector systems from

CAEV and Visna. To the best of my knowledge, the explanation for the lack of success with CAEV and Visna remains obscure and this work has been discontinued. BIV is the most complex ungulate virus and has genes that are not represented in other ungulate viruses. This, it was unexpected that BIV would yield a vector system with the high titers, breadth of tropism, and high level, sustained in vivo expression that has been seen with the system described in this application.

10. After reviewing the PCT, I found that the only real experimentation and work was done with FIV. While there is some mention of trying to extend the results from FIV to other species of lentivirus, there is no presentation of the genome organization of other lentiviruses in the PCT or explanation of the particular portions of the genome that need to be manipulated and how, as well as methods to direct me how to obtain expressing BIV vectors. This is important because the literature and my knowledge from experimentation with lentiviruses recognized that each is unique. In addition, BIV is the most distantly related lentivirus of all the lentiviruses from FIV and HIV. In fact, the PCT itself provides statements that indicate BIV is very different from FIV, there are many unaccounted for issues in making vectors from a non-primate lentivirus and there are many unaccounted for issues in having the viral vectors express a transgene in human cells. Thus, I do not believe the PCT document provides me with adequate guidance to make BIV vectors with a reasonable expectation of success.

11. Thus, a gene therapist would conclude on reading the PCT document that the results from the FIV vectors are specific for FIV because of the differences among the lentiviruses and the lack of guidance in the PCT document of how to make vectors from other non-primate lentiviruses.

12. The U.S. patent relating to the BIV genome does not suggest making BIV vectors. Moreover, the U.S. patent does not provide any guidance or direction on how to modify the BIV genome to make successful vectors that express transgenes in human cells. Thus, I do not believe the U.S. patent relating to the BIV genome provides me with adequate guidance to make BIV vectors with a reasonable expectation of success.

13. Thus, a gene therapist would conclude on reading the BIV genome patent that there is no suggestion of making vectors, and no direction on how to make BIV vectors that express a transgene in human cells with a reasonable expectation of success.

14. Finally, the Temin patent relates to BLV, which is not a lentivirus and is unrelated to BIV. Temin does not teach or suggest how to make BIV vectors.

15. Thus, a gene therapist would conclude that because BLV is unrelated to BIV, it is not likely that manipulation of BLV could successfully be accomplished in BIV.

16. Therefore, I conclude that none of the three references suggests and provides guidance for making a BIV vector that would work in human cells with a reasonable expectation of success. Even when the references are considered together, there is no direction or guidance of how to manipulate the BIV genome to obtain vectors that will express transgenes in human cells with a reasonable expectation of success. To the contrary, failure with the CAEV and Visna viruses, which are more closely related to FIV than is BIV, would suggest a high likelihood of unexpected problems that would prevent the generation of an effective BIV vector.

17. I hereby declare that all statements made herein are of my own knowledge and are true, and that all statements made on information and belief are believed to be true, and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom.

June 28, 2004
Date

Sheila Connelly
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